Associations of alkali and alkaline earth metal ions with cyclic transition states having crown-ether-like structure

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Abstract – The template effect of alkali and alkaline earth metal ions on the formation of crown ethers is believed to arise from the ability of the metal ion to organize the open chain reactant in a conformation favourable to ring closure. The template effect is conveniently discussed in terms of relative ligation abilities of reactants and transition states for ring closure. It is shown that the latter are well-behaved macrocyclic ligands, closely conforming to the ion-in-the-hole model.

INTRODUCTION

The study of associations between alkali and alkaline earth metal ions with polyether ligands is a well developed subject of interdisciplinary nature (ref. 1 and 2). Perhaps the most interesting feature is the well established concept of the fit between the cation and macrocyclic ligand cavity size, which leads to remarkable selectivities in cation associations.

It is well known that a large number of chemical phenomena are deeply and selectively influenced by coordinative interactions with alkali and alkaline earth metal ions (ref. 3). Among these, the findings that certain cations may strongly and specifically facilitate the formation of crown ethers have attracted our attention as remarkable examples of homogeneous catalysis by metal ions. It is the purpose of this lecture to review our quantitative work in the field. The systems chosen for our investigations are phenolic substrates (ArOH) having an ortho polyether side-chain bearing an ω-bromo leaving group, which under the influence of base undergo cyclisation to the corresponding benzo-3x-crown-x ethers (B3xCx).

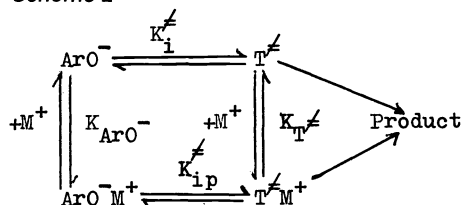$$\text{ArOH} \quad\quad\quad \text{ArO}^- \quad\quad\quad \text{B3xCx}$$

(1)
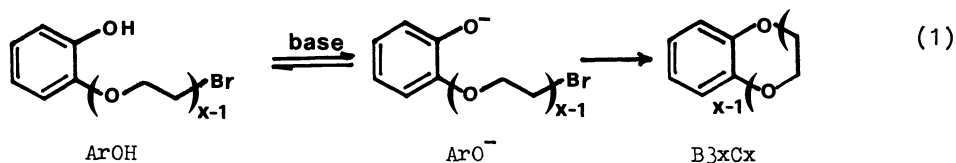
Our earliest published work in this field involved an examination of the effect of alkali (Li, Na, K) and alkaline earth (Sr, Ba) metal ions on the rate of formation of B18C6 in alkaline water solution (ref. 4). Significant rate enhancements were observed with Sr^{++}, Ba^{++}, K^+, and Na^+, but not with Li^+. Although limitations of varying nature prevented a complete analysis of the kinetic data, it was nevertheless clear that the template effect is a kinetically detectable phenomenon. Moreover, the suggestion was strong that under the conditions of the kinetic experiments a simple distribution scheme was operating, i.e., a scheme which involves a preequilibrium with 1:1 stoichiometry between ArO$^-$ and the metal ion and two parallel reaction paths. This was fully confirmed by subsequent works in MeOH and in 99% Me_2SO solution, in which more extensive investigations of reaction (1) could be carried out.

Scheme 1
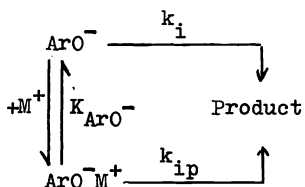
Scheme 2

Distribution scheme according
to classical kinetics.

Distribution scheme according
to transition state theory.

The influence of metal ions on the rate of the investigated reactions could
be quantitatively accounted for in terms of classical kinetics (Scheme 1) by
the hypothesis that the overall reaction rate $\underline{v}$ is given by independent
contributions from the free anion ArO^- and the ion pair ArO^-M^+, according to
eq. (2). Equation (2) is equivalent to eq. (3), where K_{ArO^-} is the
equilibrium constant for association defined by eq. (4), and
$k_{obs} = \underline{v}/([ArO^-] + [ArO^-M^+])$ is time-independent provided $[M^+]$ does not
suffer from major variations in a given run. If k_i can be directly measured
and a suitable expression for the activity coefficient γ is available, eq.(3)

$$\underline{v} = k_i[ArO^-] + k_{ip}[ArO^-M^+] \tag{2}$$

$$k_{obs} = k_i \frac{1 + (k_{ip}/k_i)K_{ArO^-}\gamma^2[M^+]}{1 + K_{ArO^-}\gamma^2[M^+]} \tag{3}$$

$$K_{ArO^-} = \frac{[ArO^-M^+]}{[ArO^-][M^+]\gamma^2} \tag{4}$$

shows that the measured k_{obs} values are related to the concentration of metal
ion through an equation with two unknown parameters, k_{ip} and K_{ArO^-}. These are
the relevant quantities which determine the magnitude of the template effect
and its dependence upon cation concentration.

According to the transition state theory, eq.(3) is equivalent to eq.(5), in
which $K_T^{\neq}$, given by eq.(6), has the meaning of the equilibrium constant for
conversion of the transition state $T^{\neq}$ that does not contain M^+ into one that
contains M^+, i.e., the ion pairing association constant of the transition

$$k_{obs} = k_i \frac{1 + K_T^{\neq}\gamma^2[M^+]}{1 + K_{ArO^-}\gamma^2[M^+]} \tag{5}$$

$$K_T^{\neq} = (k_{ip}/k_i)K_{ArO^-} \qquad \text{or} \qquad k_{ip}/k_i = K_T^{\neq}/K_{ArO^-} \tag{6}$$

state (Scheme 2). According to eq.(6) catalysis ($k_{ip} > k_i$) or inhibition
($k_{ip} < k_i$) occurs if the transition state binds cations more strongly
($K_T^{\neq} > K_{ArO^-}$) or less strongly ($K_T^{\neq} < K_{ArO^-}$) than the reactant. Thus, the
problem of the influence of the metal ion on the magnitude of the template
effect resolves itself into questions of the response to the metal ion of the
relative ligation abilities of reactant and transition state.

TEMPLATE EFFECT IN MeOH SOLUTION

Cyclisation of ArO⁻, x = 6 to B18C6 has been found to be strongly accelerated by alkali and alkaline earth bromides in MeOH solution. Direct measurement of the specific rates of reaction of the free ion and ion pairs was possible, thus providing for the first time a quantitative determination of the template effect on the formation of a macrocyclic ligand (ref. 5). At 25°C the ratio k_{ip}/k_i is 60.7 for Na^+, 199 for K^+, 48.7 for Rb^+, 17.1 for Cs^+, 51.6 for Ca^{++}, 1190 for Sr^{++}, and 334 for Ba^{++} (ref. 6). In the case of Li^+, no significant effect on the cyclisation rate was observed.

In a qualitative description of the phenomenon, the template effect is believed to arise from a greater proximity of chain ends in the metal ion associated reactant than in the unassociated one. Superimposed to the proximity effect there is an adverse chemical effect due to reduction of the inherent nucleophilicity of the nucleophilic end of ArO⁻ upon cation pairing (ref. 5).

In order to provide a sound basis for a more quantitative analysis of the template effect, we have obtained from equilibrium measurements (ref. 7) log K data for associations of the metal ions with the three polyether ligands involved in the reaction, namely, ArOH, ArO⁻, and B18C6 (Scheme 3). These are all sexadentate oxygen ligands, but belong to different structural types. Both ArOH and ArO⁻ are open chained, but a negative charge is present on the latter. Coulombic interaction of the negative charge with the positive charge(s) of the cations is expected to provide an additional driving force for association. Similarly, B18C6 is predicted to bind cations more strongly that its acyclic counterpart ArOH, in view of well established properties of multidentate ligands (macrocyclic effect, see ref. 1 and 8). The log K data plotted in Fig. 1, are consistent with expectations and provide a quantitative evaluation of the negative charge effect and of the macrocyclic effect. The stabilising effect of the negative charge amounts to 1 order of magnitude with the singly charged cations, but increases to 4-5 powers of ten with the doubly charged ones. The 18-membered macrocycle binds cations 2 to 3 orders of magnitude more strongly that its acyclic counterpart.
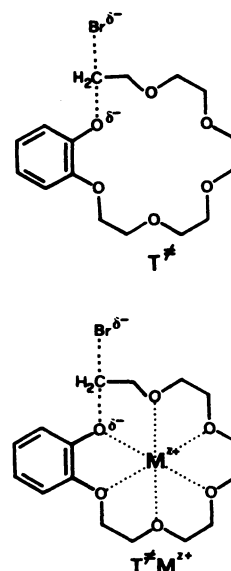
Scheme 3
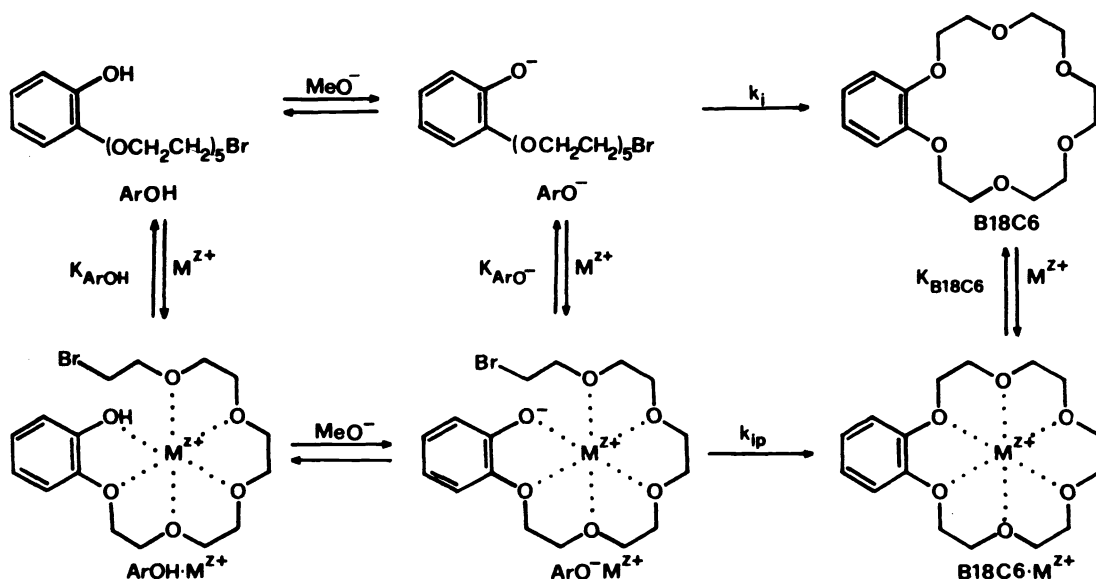
Distribution scheme involving fully coordinated structures.
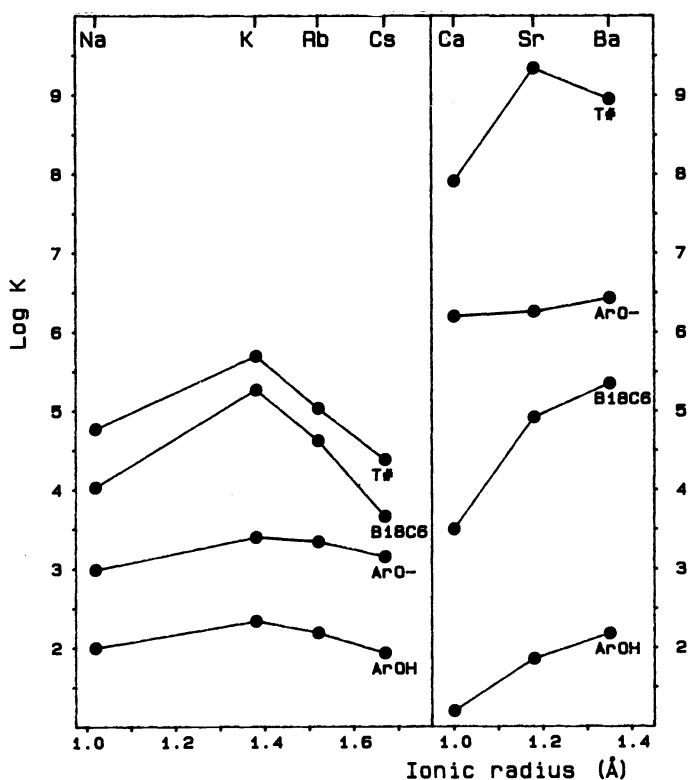
Fig.1. Log K for the association of metal ions with
the sexadentate oxygen ligands involved in the
B18C6-forming reaction in MeOH solution.

Let us now consider the ligation properties of the transition state $T^{\neq}$. The
log $K_{T^{\neq}}$ values, calculated by means of eq.(6) from the known (k_{ip}/k_i) and
K_{ArO^-} values, are plotted in Fig. 1. One first notes that the transition
state $T^{\neq}$ is the best ligand out of the four species ArOH, ArO^-, $T^{\neq}$, and
B18C6 for all of the given metal ions. This is clearly consistent with a
fully coordinated structure for the cation-paired transition state, as shown
in Scheme 4. It is remarkable that the effect of the variation of cation on
the stability of the $T^{\neq}M^{z+}$ pairs roughly parallels the effect of the

variation of cation on the stability of the $B18C6 \cdot M^{z+}$ pairs. Furthermore,
cation interactions with $T^{\neq}$ are stronger than with B18C6 because the former
is negatively charged. We note, however, that the stabilizing effect of the
negative charge tends to be stronger with the open chain ligands than with
the cyclic ones. This is written as eq.(7), in which P is 0.62 ± 0.06 for K^+,
Rb^+, Cs^+, Ca^{++}, and Ba^{++}, it is 0.25 for Na^+ and negligibly small for Sr^{++}.
If B18C6 and ArOH properly mimick hypothetical neutral ligands having the

$$\log(K_{ArO^-}/K_{ArOH}) = \log(K_{T^{\neq}}/K_{B18C6}) + P \tag{7}$$

same structure and geometry of $T^{\neq}$ and ArO^-, respectively, the quantity P is
easily interpreted as due to the loss of cation-anion interaction on going
from initial to transition state because of dispersal of the negative charge
of the latter on a three-atom-system. Equation (7) may be rewritten as eq.(8),
which shows that the template effect can be viewed as a manifestation of the
macrocyclic effect due to the fact that $T^{\neq}$ is cyclic whereas ArO^- is open

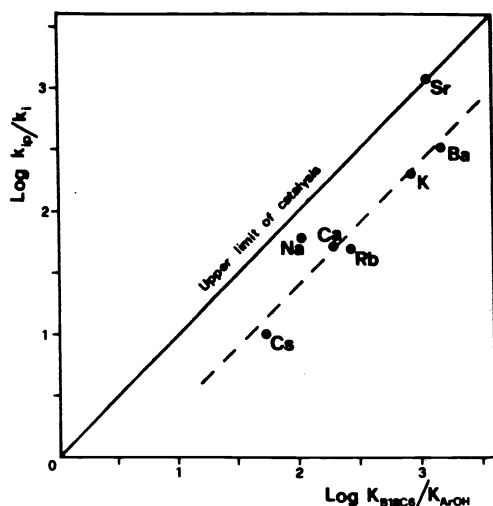$$\log(k_{ip}/k_i) = \log(K_{B18C6}/K_{ArOH}) - P \tag{8}$$

Fig. 2

Fig. 2. Catalytic effect in the formation
of B18C6 vs. macrocyclic effect in the
model system B18C6/ArOH in MeOH.
(Reproduced with permission from ref.7).

Fig. 3. Effect of tetraethylammonium and
alkali metal bromides on the rate of
the B18C6 forming reaction in 99% Me_2
SO at 25°C. The horizonatal line
represents log k_i (Reproduced with
permission from ref. 9).

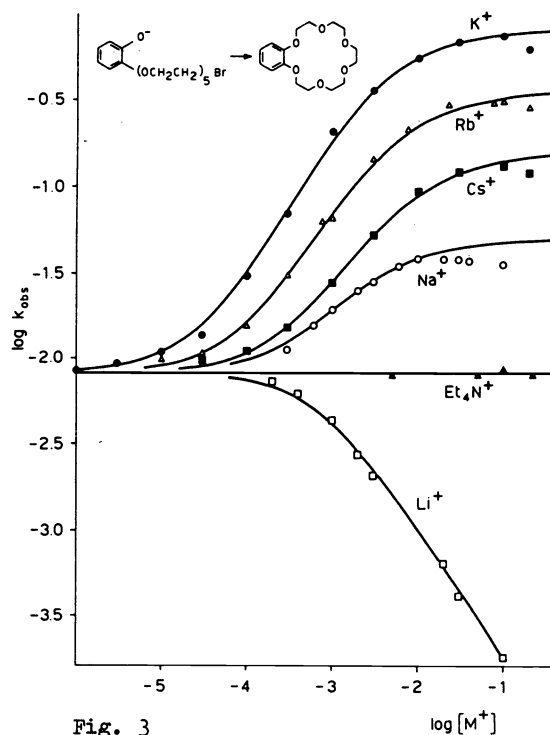
Fig. 3

chained, allowance being made for the dispersal of the negative charge on
going from ArO⁻ to T≠. A plot of $log(k_{ip}/k_i)$ against $log(K_{B18C6}/K_{ArOH})$ is
shown in <u>Fig. 2</u>. The full line with unit slope and zero intercept represents
the extent of catalysis for hypothetical templated reactions in which the
sole effect of the metal ion is to gather the reactive ends together. Thus,
within the precision of the extrathermodynamic analysis on which eq.(8) is
based, the macrocyclic effect K_{B18C6}/K_{ArOH} provides an estimate for the
proximity effect. Figure 2 shows that, apart from some deviant values, the
experimental data fall below the full line by a factor of about 4, which
provides a measure for the nucleophilicity decrease of the aryloxide end of
ArO⁻ upon cation pairing.

TEMPLATE EFFECT IN 99% Me₂SO SOLUTION

The crown-ether forming reactions are faster by about 4 orders of magnitude
in the nearly aprotic 99% Me_2SO than in the protic MeOH. In the former,
cyclisations proceed at rates convenient for extensive kinetic measurements.
<u>Fig. 3</u> shows the effect of added tetraethylammonium and alkali metal bromides
on the rate of cyclisation of 1.5×10^{-4} M ArO⁻Me₄N⁺ to B18C6 in 99% Me₂SO at
25°C (ref. 9). The close adherence of the reactions to the mechanism of Scheme
1 (or Scheme 2) is shown by the full lines calculated by means of eq.3 (or
eq.5). Whereas the rate of formation of B18C6 is depressed by Li⁺(k_{ip}/k_i<0.01)
the effect of the other alkali cations is rate enhancing, the catalytic effect
k_{ip}/k_i being 100 with K⁺, 43 with Rb⁺, 19 with Cs⁺, and 6.1 with Na⁺.
Interestingly, the K_{ArO^-} values were obtained in this case directly from the
kinetics. Independent equilibrium measurements gave a K_{ArO^-} value for
association with K⁺ coincident with that derived from the kinetics within
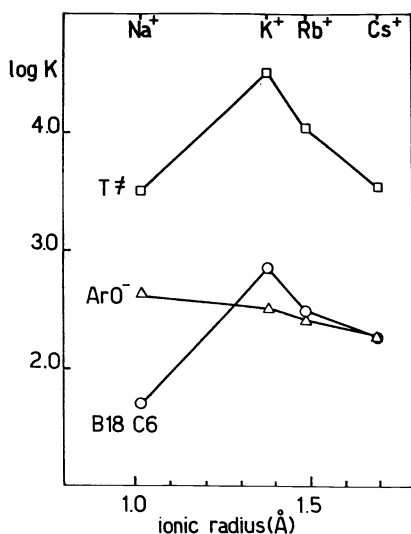experimental errors(ref. 9).

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Fig. 4. Log K for the association of
  alkali cations with reactant, tran-
  sition state, and reaction product
  in the B18C6 forming reaction in 99%
  Me_2SO at 25°C (Reproduced with per-
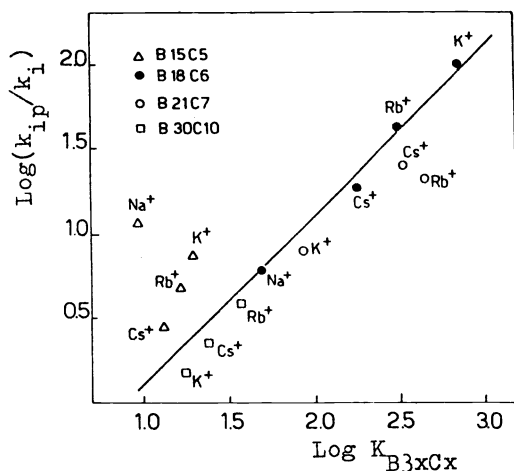 mission from ref. 9).

Fig. 5. Catalytic efficiency of the
  alkali metal ions on the crown ether
  forming reactions against association
  with the crown ether product. The slope
  of the line is 1.00 and the intercept
  is -0.90 (Reproduced with permission
  from ref. 10).

Considerable insight into the transition state structure is provided by
comparison of the log K values for the associations of the metal ions with
reactant, transition state, and reaction product (Fig. 4). Again we note that
the transition state binds the alkali metal ions much more strongly than
either the open chain reactant or the reaction product. Whereas ArO^- exhibits
poor selectivity among cations, associations with both $T^{\neq}$ and B18C6 are
markedly cation dependent and exhibit similarly structured patterns. These
findings reinforce the conclusions that the geometry of $T^{\neq}$ closely resembles
that of B18C6 and that fully coordinated structures are involved in the
cation-paired transition states.

It is unfortunate that the K_{ArOH} values are not available in 99% Me_2SO, since
we found no evidence for association with ArOH in this medium. However, if
one makes the admittedly rough assumption that the magnitude of the
macrocyclic effect K_{B18C6}/K_{ArOH} does not vary in going from MeOH to 99% Me_2SO,
on the basis of the known values in the former solvent the K_{ArOH} values in
99% Me_2SO are estimated to be nearly cation independent and in the
neighborhood of 1 M^{-1}. Therefore within the limits of the above approximation
eq.(8) reduces to the form of eq.(9), which is consistent with the free

$$\log(k_{ip}/k_i) \approx \log K_{B18C6} - P \qquad (9)$$

energy relationship shown in Fig. 5 for the B18C6 case. The negative values
of the intercept (P=- 0.90) is highly significant, since it indicates a
substantial decrease of nucleophilicity due to cation pairing, although the
absolute value cannot be taken too seriously.

It was possible to provide an independent and more reliable estimate of the
nucleophilicity decrease upon cation pairing. This was done by reference to
the intermolecular alkylation of $\underline{o}$-$^-OC_6H_4(OCH_2CH_2)_4OCH_3$ with butyl bromide

under the same conditions. It was found that the rate of this model reaction was indeed depressed by all alkali cations, the k_{ip}/k_i value being 0.07 with K^+, Rb^+, and Cs^+, 0.035 with Na^+, and less than 0.01 with Li^+. These values permitted the rate-enhancing factors due to proximity alone to be evaluated by correcting the observed catalytic factors for the nucleophilicity decrease, as shown in eq.(10), in which intra and inter refer to the B18C6 forming

$$\text{proximity effect} = \frac{(k_{ip}/k_i)_{intra}}{(k_{ip}/k_i)_{inter}} \qquad (10)$$

reaction and to the intermolecular model reaction, respectively. Introduction of the appropriate k_{ip}/k_i values into eq.(10) yields values of $10^{2.2}$ for Na^+, $10^{3.2}$ for K^+, $10^{2.8}$ for Rb^+, and $10^{2.4}$ for Cs^+.

Template effect and ring size

Since associations between alkali metal ions and crown ethers are known to be highly dependent upon the ring size of the crown ether (ref. 2), changes in the chain length x of the precursor ArO⁻ are predicted to exhibit a large variety of patterns, depending on the cation-substrate pair. An extensive study of the effect of alkali metal ions on the rate of formation of B3xCx ethers with x = 4, 5, 7, 10, and 16 has been carried out in 99% Me_2SO

(ref. 10) as an extension of that previously reported for the formation of B18C6. The rate data are plotted in **Fig. 6**, which indeed shows that each metal ion gives rise to a differently structured profile which is highly dependent on the size of the ring to be formed. Whenever possible, log K_{B3xCx} data in 99% Me_2SO have been obtained (**Fig. 7**). Comparison with Fig. 6 indicates that there is a close similarity between structure effects on rates and structure effects on associations with the crown ether products. This is well shown by a plot of $\log(k_{ip}/k_i)$ vs. log K_{B3xCx} for all cation-substrate pairs for which data are available (Fig. 5). According to the simple model
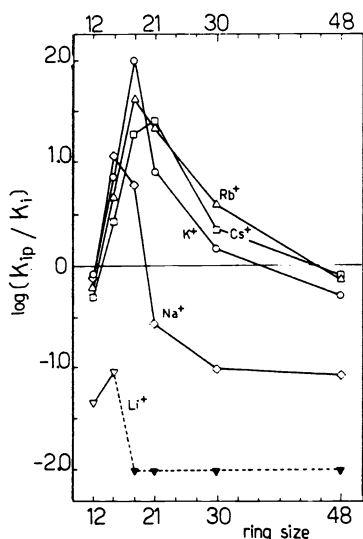

Fig. 6. Catalysis and inhibition by alkali cations on the formation of benzo crown ethers in 99% Me_2SO at 25°C. The full triangles represent upper reactivity limits (Reproduced with permission from ref. 10).
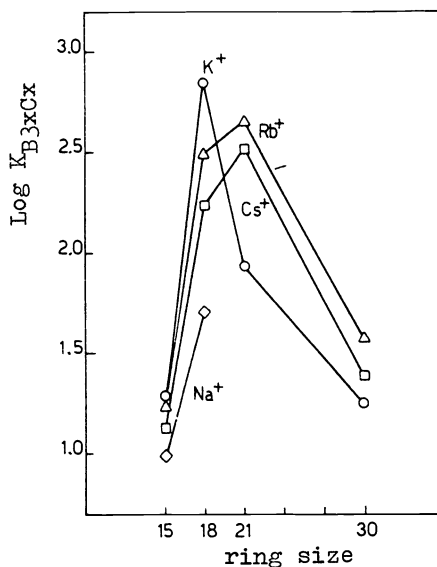
Fig. 7. Association of alkali cations with benzo crown ethers in 99% Me_2SO at 25°C (Reproduced with permission from ref. 10).

which assigns to the M^+-paired transition states the geometries of the corresponding M^+-crown ether complexes, all the points in the plot of Fig. 5 should lie on the same line. This is clearly not the case, but an unmistakable trend is present, showing that a metal ion which associates strongly with a crown ether is also a good catalyst for the formation of that crown ether, and that the magnitude of the template effect is basically related to those factors which govern the strength of association with the reaction product.

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